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Effects of Tetrandrine and QYT on ICAM-1 and SOD gene expression in pancreas and liver of rats with acute pancreatitis

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Abstract

AIM: Available experimental evidence from both clinical and animal models shows that both Chinese medicines tetrandine (Tet) and Qing Yi Tong (QYT) have positive treatment effects on acute pancreatitis (AP). This investigation was conducted to explore the treatment mechanisms of Tet and QYT on AP at the molecular level and thereby explain their therapeutic affects. It included an investigation of the effects of these drugs on gene expression of both intercellular adhesion molecule 1 (ICAM-1) and superoxide dismutase (Mn-SOD and Cu, Zn-SOD) in a rat model with AP.

METHODS: AP in the test rats was induced by subjecting them to laparotomy followed by a retrograde injection of 4 % sodium taurocholate into the bilio-pancreatic duct. The test rats with AP were divided into three groups. One was treated with Tet, one with QYT, and one with normal saline solution. The sham-operated control group (SO) rats were only subjected to laparotomy. They were given no further treatment. For the Tet group, Tet was injected intraperitoneally, and for the QYT group, QYT was given with a nose-gastric catheter. These procedures were done at both 10 min and 5 h after AP induction. The levels of ICAM-1 mRNA expression and of SOD (Mn-SOD and Cu, Zn-SOD) mRNA expression in the pancreas and liver tissues were measured by RT-PCR at 1, 5, and 10 h after AP induction.

RESULTS: When compared with the SO group during the observation time, rats with AP showed a higher expression of ICAM and a lower expression of Mn-SOD in both pancreas and liver tissues, and a lower expression of Cu, Zn-SOD in the pancreas. Tet treatment attenuated changes in the expression of both ICAM-1, and SOD (Mn-SOD and Cu, Zn-SOD) to a significant degree. A similar effect on the expression of SOD (Mn-SOD and Cu, Zn-SOD) was also found in the QYT group, but no obvious suppressive effect on ICAM-1 expression was observed.

CONCLUSION: The results of this study suggest that one of the main mechanisms of Tet and QYT in treating AP is to enhance anti-oxidation of the body. The results also suggest that the anti-inflammatory effect of Tet is

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involved in the reduction of ICAM-1 expression. This explains why Tet and QYT are beneficial in treating AP.

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INTRODUCTIONAcute pancreatitis (AP) is a severe disease with both high morbidity and high mortality. Therefore, much research has been focused on the specific and effective therapies for AP[1-6]. Tetrandrine (Tet) is a kind of dibenzyl quinoline alkaloid extracted from the root of Stephania tetrandra S., a Chinese herbal medicine. Qing Yi Tang (QYT) is a medicine composed of several Chinese herbs. Both Tet and QYT have shown positive treatment effects on AP clinical patients and on animal models. These include attenuation of clinical symptoms, improvement of morphology and biochemistry changes in the tissues and blood, prolongation of survival time, and decrease of mortality[7-10]. In order to explore some of the molecular mechanisms combating AP, the effects of Tet and QYT on gene expression of both intercellular adhesion molecule 1 (ICAM-1) and superoxide dismutase (Mn-SOD and Cu,Zn-SOD) were investigated in a rat model with AP.

MATERIALS AND METHODS

Chemicals

Chemicals used in this experiment were purchased as follows: Sodium pentobarbital and sodium taurocholate (NaTc) from Shanghai Chemical Reagent Company; TRIzol reagent and Superscript™ II from GIBCO-BRL (Shanghai); Oligonucleotide primer pairs from Chinese Academy of Science, Institute of Cell and Biology (Shanghai); Taq DNA polymerase from Promega (Shanghai); Tet from the Department of Pharmacology of Second Military Medical University (Shanghai); QYT from Zunyi Medical College (Zunyi); other reagents from Sigma Chemical (Shanghai).

Animals and AP model

The subjects for the experiment were adult male and female Sprague-Dawley rats weighing 170-230 g (n=36; the Animal Center, Fudan University Medical College, Shanghai). After fasting with free access to water overnight, the rats were anesthetized by an intraperitoneal (ip) injection of 40 mg/kg sodium pentobarbital. AP was induced by a retrograde injection of 4 % NaTc into the bilio-pancreatic duct (BPD) according to the method of Aho *et al*[11]. Briefly, a small median laparotomy was performed first, and then the pancreas was exteriorized and the BPD was temporarily closed at the liver hilum with a soft microvascular clamp to prevent reflux of the infused material into the liver. A retrograde injection of 4 % NaTc into the distal BPD was then given (100 ul/100body wt, pressure 50cmH_2O). The clamp was removed 5 min after the injection. In the sham-operated control group (SO) rats only underwent laparotomy. Finally, the abdomen was closed with a silk suture and the rats were placed back into their cages with free access to water and food.

Animal group

The test rats with AP were divided into three groups: Tet, QYT and normal saline (NS). The Tet group (n=9) received an injection (ip) of 4 %Tet at a dosage of 80 mg/kg body wt. The QYT group (n=9) received an infusion of QYT (1 ml/100 g body wt), and the NS group (n=9) received an infusion of NS (1 ml/100 g body wt), by use of a nose-gastric catheter. Rats in the SO group received the same infusion as the NS group. All groups were treated two times (at 10 min and 5 h after the AP operation).

Preparation of RNA and RT-PCR assay

At selected times (1,5,10 h) after the AP induction or sham operation, the rats (n=3 at each time point) underwent relaparotomy under pentobarbital anesthesia, and samples of the pancreas and liver were rapidly collected. Total RNA was extracted from pancreatic and liver tissues using the TRIzol reagent. RNA quality was verified by ethidium bromide staining of ribosomal RNA bands on agarose gel. Total RNA was precipitated and re-suspended in diethylpyrocarbonate-treated sterile H_2O, quantified by spectrophotometry (A260/A280 ratio >1.80) and diluted to a concentration of 1.0 mg/ml. Then the extracted RNA was used for a semi-quantitative reverse transcription-polymerase chain reaction (RT-PCR). Total RNA (5 mg/sample) was reverse-transcribed using oligo (dT) as a primer. The oligonucleotide primer pairs were designed from published sequences for each gene studied. The sequences used as G3PDH, SOD and ICAM-1 specific primers are shown in Table 1.

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Table 1 Sequence of primers and length of fragments

Gene	Primer (5'→3')	Length
G3PDH	ACCACAGTCCATGCCATCAC	452 bp
	TCCACCACCCTGTTGCTGTA	
Mn-SOD	ATTAACGCGCAGATCATGCAG	483 bp
	TTTCAGATAGTCAGGTCTGACGTT	
CuZn-SOD	TTCGAGCAGAAGGCAAGCGGTGAA	396 bp
	AATCCCAATCACACCACAAGCCAA	
ICAM-1	CCTTAGGAAGGTGTGATATCCGG	415 bp
	AGGTGGTCACCCATGCTGGTGCT	

Two-microliter aliquots of cDNA were used as a target for separate PCR reactions in the presence of 0.5 units of Taq DNA polymerase, 50 μmol/L of a primer pair specific for G3PDH, SOD or ICAM-1, and amounts of the corresponding constructs. The total volume of the reaction fluid was 25 μl.

The amplification cycles were carried out in a DNA Thermalcycler (Perkin Elmer) under the following conditions: initial denaturation at 94 for 2 min, followed by amplification cycles of 1min at 94 ℃, 1min at 58 ℃ and 1 min at 72℃. This procedure was repeated for 30 cycles. PCR products were separated by polyacrylamide gel electrophoresis and then visualized by ethidium bromide staining. The intensities of gene-specific bands were photographed and quantified by measuring the optical density (OD) of the bands in a UVP (white/UV transilluminator, GDS 7500). In the same sample, mRNA levels were normalized to the density of an internal control housekeeping gene RT-PCR product, glyceraldehyde-3-phosphate dehydrogenase (G3PDH), which is commonly used as an internal standard control in mRNA expression studies. RT-PCR was performed independently at least twice starting from the same RNA.

Statistical analysis

Data were expressed as mean ±SE. Statistical differences between values from two groups were determined by the unpaired Student's *t*-test and statistical significance was set at $P<0.05$.

RESULTS

G3PDH level

The level of G3PDH was approximately the same for all pancreas and liver samples tested (Figure 1), which indirectly showed that the cDNA concentration did not differ in the samples from each group.

Figure 1 GAPDH mRNA expression in the liver in the parts of different group.

ICAM-1 mRNA expression in the pancreas and liver

Semi-quantitative evaluation of ICAM-1 level was obtained by measuring its gene expression by RT-PCR. As shown in Figure 2 and Figure 2B, the pancreas showed an increased ICAM-1 mRNA expression in the NS group at 5 h and 10 h after AP induction when compared to the SO group. Tet attenuated the increase at the same time-points. But QYT showed an increase effect for ICAM-1 mRNA expression at 10 h after AP. In the liver, compared with the SO group, the level of ICAM-1 mRNA expression in the NS group was elevated at 1 h and sustained up to 10 h, with a maximum increase (2-fold) at 5 h after AP induction. A similar change but at a lower level was observed in the Tet group. And in the QYT group a modest increase of ICAM mRNA expression occured only at 5 h and 10 h after AP induction. (Figure 3 and Figure 3B).

Figure 2A (PDF) ICAM-1 mRNA expression in the pancreas in the different groups.
Figure 2B ICAM-1 mRNA expression in the pancreas in the different groups.
Figure 3A (PDF) ICAM-1 mRNA expression in the liver in the different groups.
Figure 3B ICAM-1 mRNA expression in the liver in the parts of different groups.

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Mn-SOD mRNA expression in the pancreas and liver

As shown in Figure 4 and Figure 4B, in the pancreas, compared to the SO group, Mn-SOD mRNA expression in the NS group was lower from 1 h to 5 h after AP induction. The Tet-treated group had a higher expression at the same time-points, and the QYT-treated group had a much higher expression at 10 h, nearly a 2-fold increase compared to that of the NS group. As shown in Figure 5 and Figure 5B, the NS group showed a similar decrease of Mn-SOD mRNA expression in the liver to that in the pancreas at 1 h and 5 h. When compared to the NS group, the Tet-treated group had a higher Mn-SOD mRNA expression from 1 h to 10 h, and the QYT group had a higher Mn-SOD mRNA expression from 5 h to 10 h, after AP induction.

Figure 4A (PDF) Mn-SOD mRNA expression in the pancreas in the different groups.
Figure 4B Mn-SOD mRNA expression in the pancreas in the parts of different groups.
Figure 5A (PDF) Mn-SOD mRNA expression in the liver in the different groups.
Figure 5B Mn-SOD mRNA expression in the liver in the parts of different groups.

Cu,Zn-SOD mRNA expression in the pancreas and the liver

As shown in Figure 6 and Figure 6B, in the pancreas, the NS group decreased significantly in Cu, Zn-SOD mRNA expression after AP induction to 1/3 of that in SO group. The Tet and QYT- treated groups had much higher levels of Cu,Zn-SOD mRNA expression at 1 h and 10 h respectively. These high levels were a 2-fold increase when compared with the SO group, and a 4-fold increase when compared with the NS group at the same time points. In the liver, no obvious changes of SOD expression were observed (Figure7).

Figure 6A (PDF) Cu, Zn-SOD mRNA expression in the pancreas in the different groups.
Figure 6B Cu, Zn-SOD mRNA expression in the pancreas in the parts of different groups.
Figure 7 Cu, Zn-SOD mRNA expression in the liver in the parts of different groups.

DISCUSSION

Research on AP can be traced back at least one hundred years, yet the treatment of AP continues to be a difficult aspect of clinical practice, especially for severe acute pancreatitis (SAP). SAP is recognized to be a multiple-stage disease where the pathological events at the pancreatic acinar cell level are paralleled by an exaggerated local and systemic inflammatory response (SIRS), and even by multiple-organ damage (MODS) or failure (MOF), with a high mortality[12-15]. Considerable progress in understanding of pathophysiologic events during the early stage of AP has been made over the years, but the underlying pathogenic processes responsible for the inflammatory cascade and MOF are still unknown to a large extent. Most recent studies have revealed that the excessive releases of oxygen-derived free radicals (OFRs), destructive inflammatory mediators and cytokines, such as TNF-alpha, IL-1beta, IL-6, IL-8, IL-10, PAF, ICAM-1, play key roles in the AP process[16-19]. Recent evidence suggests that, besides their directly detrimental effects on AP, OFRs may activate certain gene transcription factors, notably the nuclear transcription factor-kappa B (NF-kB) and activator protein-1 (AP-1), which then mediate the induction of certain adhesion molecules (ICAM, VCAM, etc,) and other cytokines[15,20-23]. These factors prompt neutrophil aggregation, adherence and activation, then tremendous amounts of inflammatory mediators and cytokines are released. The pancreas and remote organs are then severely injured and MOF occurs. Meanwhile, activation of leukocyte may release more OFRs, and the vicious circle continues[24-27].

The manganese superoxide dismutase (Mn-SOD) and copper/zinc superoxide dismutase (Cu, Zn-SOD) existing in the mitochondria or cytoplasm of cells are the major OFR scavengers of the body. Previous experiments have demonstrated that the pathological changes in AP could be reduced by SOD[28,29]. By immunohistochemistry, Su *et al* have proved the localization of SOD in acinar cells and have found Mn-SOD mRNA expression peaked at 2 hours after the addition of arginine to the cell culture medium[30]. These data suggest that increased SOD expression reflects a defensive mechanism of acinar cells against oxidative stress. G. Teleck *et al* discovered that the increase of OFRs and ICAM expression could be measured within one hour and lasted for the 24 hour observation period[31]. These findings, along with others from different laboratories, suggest that OFRs and ICAM induce morphologic change, aggregation, adherence, and activation of polymorphonuclears (PMNs), which then shift out of blood vessels and consequently cause microcirculation dysfunction[32,33]. Our experimental results showed that during the process of AP, the expression of ICAM-1 in both the pancreas and the liver (especially in liver) was significantly increased, while the expressions of Mn-

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SOD and Cu-Zn-SOD were decreased in the pancreas by 1/3 as compared to the SO control group.This was similar to the finding of the experiment by L. Czako *et al*[28]. These results provide further evidence that the increased ICAM-1 and decreased OFRs scavengers take part in the pathophysiologic processes of AP.

Tet is a kind of dibenzyl quinoline alkaloid extracted from the root of Stephania tetrandra S., a Chinese herbal medicine with the effect of a non-selective calcium channel blocker (CCB). It has recently been found that Tet also has a widely anti-inflammatory effect by reducing the activity of PLA2 from inflammatory leukocytes, inhibiting the release of inflammatory mediators, eliminating OFRs and dilating blood vessels, and then improving microcirculation function of the body[7,8,34,35]. QYT is a combined medication of Chinese herbs containing Rheum officinale Baillon, ructus gardeniae, etc., and also has the effects of anti-inflammation, cleaning OFRs, eliminating hazardous metabolite, dilating blood vessels and improving microcirculation[9,10]. We found in this experiment that Tet reduced ICAM expression in the pancreatic and hepatic tissues during AP, while increasing the expression of Mn-SOD, and Cu, Zn-SOD. QYT had no significant effect on the expression of ICAM-1, but significantly enhanced the expression of Mn-SOD, and Cu, Zn-SOD. These findings suggest that Tet and QYT demonstrate the potentially useful effects of eliminating OFRs and reducing their damage, and also demonstrate the ability of Tet inhibiting ICAM production. The experiment provided a molecular level explanation of why clinical treatment of AP using Tet and QYT has been successful.

It is generally recognized that the induction of AP follows a uniform mechanism independent of different etiologic causes such as gallstones, alcohol, ischemia, hyperlipidemia, hypercalcemia, heredity and others. Firstly, each cause seems to affect primarily the acinar cell, resulting in intracellular activation of trypsinogen and other digestive enzymes and over-production of OFRs, which injure the acinar cells and pancreatic tissue. Then tremendous amounts of inflammatory mediators and cytokines, mentioned above, are released into the tissue and result in microcirculation disturbance. This not only worsens the local damage, but also influences the remote organs and causes systemic inflammatory response syndrome (SIRS). In the final stage of the pathophysiological process, multi-organ damage develops and multi-organ failure (MOF) may happen due to the combined effects of all the factors. Klar *et al* pointed out[36] that since the initial enzyme activation and cytokine release were irreversible by the time of clinical presentation, specific therapy must be directed towards microperfusion failure as a secondary pathogenic stage. The beneficial therapeutic principles of this included the inhibition of leukocyte-endothelium interaction with ICAM-1 antibodies and the control of local vasoconstriction to stop the progression of the disease. Therefore, based on previously observed clinical effects and on the experimental results with Tet and QYT in this study, we conclude that Tet and QYT which inhibit ICAM-1 and enhance SOD expression are beneficial in treating AP.

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